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| EXAMINER | |
|---|---|
| JUEDES, AMY E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/530,108 | TRASCIATTI ET AL. | |
| | Examiner | Art Unit | |
| | Amy E. Juedes, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's amendment, filed 7/20/07, is acknowledged.

Claims 5, 9, 13, 15-16, 19-21, and 23 have been amended. Claims 1-24 are pending.

2. Applicant's election of group I, claims 1-16 and 19-23, drawn to a process for the expansion of TALL lymphocytes, in the reply filed on 7/20/07 is acknowledged. Applicant has further elected TALL-104 as the species of lymphocyte. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 17-18 and 24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-16 and 19-23 read on the elected invention and are being acted upon.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite in the recitation of a process for the "expansions" of TALL lymphocytes. The claim is unclear, since it is grammatically incorrect. Furthermore, claim 1 is drawn to a method of expansion of TALL lymphocytes, but the only recited step is growing cells in a single fermentation unit. It is unclear how growing any generic "cell" could result in the expansion of TALL lymphocytes (i.e. the claims do not require that TALL lymphocytes be grown). The claims don't even require growing lymphocytes.

B) Claim 2 is indefinite in the recitation of a fermentation unit "for anchorage dependent cells". The metes and bounds of the fermentation unit of the claim cannot be

established. For example, any type of unit can be used "for" anchorage dependent cells. Do the claims require a fermentation unit that allows the attachment of anchorage dependent cells?

C) Claims 4 and 7 contain the trademarks/trade names CELL-FACTORY™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name.

D) Claims 8-9 are indefinite in the recitation of cells that are TALL-104, TALL-107, TALL-103/2 cell lines, "optionally genetically modified". A cell is either a TALL-104 cell line, or a genetically modified TALL-104 cell line. It is unclear how a cell can simultaneously be a TALL-104 cell and also be genetically modified.

E) Claim 5 recites the limitation "the homogeneous system" in line 2. There is insufficient antecedent basis for this limitation in the claim, or in claims 1 and 3.

F) Claim 6 recites the limitation "the inoculum" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, or in claims 1 and 5.

G) Claim 6 recites the broad recitation of an inoculum of at least $0.7 \times 10^6$ cells/ml, and the claim also recites that the inoculum is equal to $0.75 \times 10^6$ cells/ml, which is the narrower statement of the range/limitation. Claim 6 also recites the broader recitation a harvest cell density lower than $2 \times 10^6$ cells/ml, and the claim also recites that the density is less than $1 \times 10^6$ cells/ml, which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and

Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

H) Claim 10 and 20 recite the broad recitation of 10% maximum human serum, and the claim also recites that serum concentration is 4 to 6% or 5%, which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

I) Claims 10 and 20 recite the limitations "the complete culture medium" and "the cell factory" in lines 1-2. There is insufficient antecedent basis for these limitations in the claims, or in independent claim 1.

J) Claim 12 recites the limitation "the homogeneous system" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, or in claims 1 and 10.

K) Claims 14 and 22 recite the limitation "the bag filling collet" in line 2. There is insufficient antecedent basis for this limitation in the claims, or in claims 1, 13, or 21.

L) Claim 23 recites the limitation "the process for the preparation of a therapeutic dose" in line 1. There is insufficient antecedent basis for this limitation in the claim, or in claim 20.

4. Claims 13-14, 16, and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The claims are incomplete for omitting essential steps. While all of the technical details need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. In the instant case, the claims are drawn to a process for the preparation of frozen bags of TALL lymphocytes, however, the only recited method step is growing said lymphocytes in homogenous conditions in a single fermentation unit. Thus, it is unclear how the method could result in the production of a frozen bag of lymphocytes.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10, 12-13, 15-16, 19-21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visonneau et al., 2000, in view of Gambacorti-Passerini et al., 1988.

Visonneau et al. teach a method of preparing a therapeutic dose of the human killer cell line TALL-104 comprising expanding TALL-104 lymphocytes in T175 flasks in medium supplemented with 10% fetal bovine serum and 100 U/ml of IL-2 (i.e. an antibiotic free culture medium, see page 1745 in particular). Visonneau et al. also teach freezing the TALL-104 lymphocytes, and testing the frozen cells for sterility, purity, and contamination (i.e. performing quality control assays, see page 1746 in particular).

Visonneau et al. do not teach growing at least 1 x $10^9$ cells in a CELL-FACTORY™, nor using culture medium comprising human serum.

Gambacorti-Passerini et al. teach a method for the large scale production of lymphocyte killer cells comprising culturing the cells at a concentration of 1.5x$10^6$ cells/ml in a total volume of 3500 ml in a 10 floor multitray CELL FACOTRYTM for 4 days (i.e. culturing at least 1 x $10^9$ cells, see page 524 in particular). Gambacorti-Passerini et al. teach that the procedure results in the recovery of 63% of the starting cells at the end of culture (i.e. less than 2 x $10^6$ cells/ml at harvest time, and at least 1 x $10^9$ total cells, see Table 6 in particular). Gambacorti-Passerini et al. also teach that the killer lymphocytes can be grown in range of concentrations (2.5%, 5% or 10%) of homologous human serum without affecting cell recovery (see page 525 in particular). Gambacorti-Passerini et al. also teach harvesting the lymphocytes into bags, and freezing the bags (see page 524-525 in particular). Gambacorti-Passerini et al. also teach that the large scale production of the killer cells in the CELL-FACTORY™ results in fully comparable activation and function of the cells compared to cells grown in standard flasks (see page 527 in particular). Gambacorti-Passerini et al. also teach that the culture method using the CELL-FACTORY™ is faster and more affordable than other cell culture methods (see page 529 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to prepare a therapeutic dose of TALL-104 killer lymphocytes, as taught by Visonneau et al., using the large scale cell culture technique taught by Gambacorti-Passerini et al. The ordinary artisan at the time the invention was made would have been motivated to make do so, since Gambacorti-Passerini et al. teach that the culture method using the CELL-FACTORY™ is faster and more affordable than other cell culture methods. Furthermore,

the ordinary artisan would have had a reasonable expectation of success since Gambacorti-Passerini et al. teach that the CELL-FACTORY™ culture system results in fully comparable activation and function of the killer lymphocytes compared to culture methods using standard flasks. Moreover, the ordinary artisan would have been motivated, and have a reasonable expectation of success in substituting the homologous human serum taught by Gambacorti-Passerini et al. for the fetal bovine serum taught by Visonneau et al., since the cells of Visonneau et al. are used for human therapy, and homologous serum would be expected to be to avoid any potential for an adverse response to foreign bovine proteins in human patients. Additionally, it would have been obvious to perform a pre-expansion of the TALL-104 killer cell lines in flasks, as taught by Visonneau et al., to obtain the appropriate number of cells for inoculating the CELL-FACTORY™. Said pre-expansion using 1.5 x $10^6$ cells/ml in a T-175 flask (typically holding ~40-90 mls volume), would result in approximately 0.7 to 1 x $10^8$ cells per flask.

7. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Visonneau et al., 2000 and Gambacorti-Passerini et al., 1988 as applied to claims 1-10, 12-13, 15-16, 19-21, and 23 above, and further in view of Woolley et al., 2000.

The combined teachings of Visonneau et al. and Gambacorti-Passerini et al. are discussed above.

They do not teach adding IL-2 to the cell cultured every 48-96 hours.

Woolley teaches that cytokine receptor expression by the cells in culture contributes to cytokine depletion of the medium (see pg. 71 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add additional IL-2 at the midpoint of the 4 day culture made obvious by Visonneau et al. and Gambacorti-Passerini et al. (i.e. at 48 hours) to further enhance the growth and expansion of the killer cells. The ordinary artisan at the time the invention was made would have been motivated to add IL-2 during the course of the culture, since Woolley et al. teach that cytokines are depleted from the medium by cytokine receptor expressing cells.

8. Claims 14 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visonneau et al., 2000 and Gambacorti-Passerini et al., 1988 as applied to claims 1-10, 12-13, 15-16, 19-21, and 23 above, and further in view of U.S. Patent 6,491,678.

The combined teachings of Visonneau et al. and Gambacorti-Passerini et al. are discussed above.

They do not teach creating a sampling chamber in the frozen bags for the purpose of performing quality controls.

The '678 patent teaches a freezing bag that can be sealed to create sample chamber that can be detached without thawing for testing the suitability of the frozen cells (see column 3 in particular). The '678 patent teaches that the sample chamber can comprise up to 1 ml (see column 9 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create a detachable sample chamber comprising up to 1 ml, as taught by the '678 patent, in the method of freezing the killer cells in bags, made obvious by Visonneau et al. and Gambacorti-Passerini et al. The ordinary artisan would have been motivated to do so, since Visonneau et al. teach testing the frozen killer cells for quality purposes, and the '678 patent teach a convenient detachable chamber than can be used to test frozen cells without having to thaw the frozen bag.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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